

Hematopoietic stem cell transplantation in a patient with osteopetrosis and mutation in CLCN7: long-term follow-up

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Abstract

Background: Osteopetrosis is a rare hereditary bone dysplasia characterized by insufficient osteoclast activity that results in increased bone mineral density. Hematopoietic stem cell transplantation (HSCT) can reverse skeletal abnormalities and restore hematopoiesis. **Case report:** We present the case of a 3-year and 2-month-old male patient with the diagnosis of osteopetrosis. The patient underwent allogeneic HSCT (Allo-HSCT) using 100% compatible bone marrow from a related donor and received a myeloablative conditioning regimen and a CD34 cell dose ($4.7 \times 10^7/\text{kg}$). In the early post-transplant, frequent complications such as pneumonitis, hypercalcemia, and hyperphosphatemia occurred. With a suitable granulocytic graft and chimerism of 100%, it was considered a successful transplant. However, the patient showed a delayed platelet graft treated with a platelet-stimulating factor for 6 months. The patient is currently disease-free, outpatient follow-up, with no data on graft-versus-host disease, and no progressive neurological damage. **Conclusions:** Osteopetrosis is a childhood disease that requires clinical suspicion and early diagnosis. HSCT is necessary at an early age to prevent disease progression and sensorineural, hematological, and endocrinological functions damage that can lead to death.

Key words: Osteopetrosis; Hematopoietic stem cell transplantation; Bone marrow stem cell transplant.

Trasplante de células progenitoras hematopoyéticas en un paciente con osteopetrosis y mutación en CLCN7: seguimiento a largo plazo

Resumen

Introducción: La osteopetrosis es una displasia ósea hereditaria poco común, caracterizada por una actividad osteoclástica deficiente que aumenta la densidad mineral ósea. Se considera que el trasplante de células progenitoras hematopoyéticas (TCPH) puede revertir las anomalías esqueléticas y restaurar la hematopoyesis. **Caso clínico:** Se presenta el caso de un paciente de sexo masculino, de 3 años y 2 meses de edad, con diagnóstico tardío de osteopetrosis. Se realizó un TCPH alogénico de donador relacionado 100% compatible con médula ósea. Se utilizaron un régimen de acondicionamiento mieloablativo y una dosis celular de CD34 de $4.7 \times 10^7/\text{kg}$ de peso. En el postrasplante temprano, el paciente desarrolló complicaciones como neumonitis, hipercalcemia e hiperfosfatemia. Con un injerto granulocítico adecuado y quimerismo del

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100% se consideró un trasplante exitoso. Sin embargo, el paciente presentó retraso en el injerto plaquetario, por lo que se administró factor estimulante de plaquetas por 6 meses. Actualmente el paciente se encuentra libre de enfermedad, en seguimiento ambulatorio, sin datos de enfermedad del injerto contra el hospedero y con pruebas de neurodesarrollo sin deterioro neurológico progresivo. **Conclusiones:** La osteopetrosis es una enfermedad infantil que requiere una sospecha clínica y un diagnóstico temprano, ya que es necesario un TCPH a corta edad como tratamiento para evitar la progresión de la enfermedad y el deterioro de las funciones neurosensoriales, hematológicas y endocrinológicas que puede derivar en la defunción del paciente.

Palabras clave: Osteopetrosis. Trasplante de células progenitoras hematopoyéticas. Trasplante de médula ósea.

Introduction

Osteopetrosis, also known as marble bone disease, is a rare hereditary bone dysplasia characterized by a decreased resorptive activity of osteoclasts leading to inadequate resorption and abnormal bone turnover, causing an increased bone mineral density and increased risk of fractures¹. Inadequate bone remodeling produces skeletal deformities, and the lack of bone elasticity coupled with bone fragility increases the risk of fractures². The endochondral bone in the medullary cavity alters hematopoietic function causing life-threatening anemia, thrombocytopenia, and leukopenia.

Alterations in bone restructuring, which produce a narrowing of the bone canals and limits blood supply, can cause neurological disorders³. Different gene mutations can cause neurological alterations: the mutation of the T-cell immune regulator 1 (TCIRG1) gene causes neuronal compression, while the mutation of the CLCN7 gene causes significant progressive encephalopathy and retinopathy in some patients⁴.

Clinical suspicion is essential to achieve early diagnosis and timely intervention with allogeneic hematopoietic stem cell transplantation (Allo-HSCT), a curative treatment that can reverse skeletal abnormalities and restore hematopoiesis⁵.

Epidemiology

Autosomal recessive osteopetrosis incidence is 1 in 250,000 births, with a higher incidence in Costa Rica (3.4 in 100,000 births). In contrast, autosomal dominant osteopetrosis incidence is 1 in 20,000 births⁶.

Classification

Osteopetrosis has a broad clinical spectrum: from a minimal disease, even asymptomatic, to the severe form known as infantile or malignant osteopetrosis (autosomal recessive), which is life threatening, especially during the first year of life (Table 1).

For decades, before identifying gene mutations affecting osteoclasts activity, osteopetrosis had been categorized depending on clinical characteristics and inheritance patterns. The *malignant* or *infantile* osteopetrosis with autosomal recessive inheritance pattern is the most severe form and the one with the earliest presentation. *Intermediate* osteopetrosis also has an autosomal recessive inheritance pattern, and *benign* or *adult* osteopetrosis is inherited in an autosomal dominant pattern.

Clinical description

The increase in bone mineral density results in particular physical characteristics, such as macrocephaly, craniofacial deformities, and generalized sclerosis. However, the primary involvement is in the bone marrow and central nervous system. The bone marrow's infiltration produces bone marrow failure; thus, hematopoiesis is compromised, and extramedullary hematopoiesis appears, which manifests itself as hepatosplenomegaly.

Etiology

Osteopetrosis is caused by a failure in osteoclasts' development and function. Furthermore, mutations in at least 10 genes are found in approximately 70% of patients. This disorder has an autosomal dominant or autosomal recessive inheritance pattern, being the last one the most severe form of presentation⁷.

Osteoclasts are highly specialized cells derived from mononuclear precursors from the myeloid lineage. Their function is bone resorption, a fundamental process for remodeling and maintaining bone stability and mineral homeostasis.

Some osteopetrosis cases are caused by mutations in genes involved in pH acidification, which depends on the proper function of V-ATPase and CLCN-7. Homozygous mutations in these genes can cause malignant osteopetrosis.

Table 1. Characteristics of the different types of osteopetrosis and genetic classification

Population	Inheritance	Bone marrow failure	Diagnosis	Clinical features	Prognosis	Associated genes (% of presentation)	Life expectancy
Adult	AD	No	Incidental	Asymptomatic. However, in type I, there is skull affection, and in type II, there is the involvement of the cranial base, vertebrae, pelvis, and long bones. In some cases, bone pain or fractures have been reported	Good	CA II RANKL	Normal
Childhood	AR	Severe	One year of age	Blindness, hearing loss, growth retardation, frequent fractures, severe hypocalcemia, hydrocephalus, neurodegeneration	Poor	TCIRG1 (51-53%)* CLCN7 (13-16%)** OSTM1 (2-6%)*	0-10 years 0-3 years 0-2 years
Intermediate	AR	Variable	Childhood/adolescence	Bone pain, arthritis, blindness, hearing loss, osteomyelitis, anemia	Variable	PLEKHM1 CLCN7 LRP5 CA II	Variable
<i>Gene and transcript</i>	<i>Location</i>	<i>Variant</i>			<i>Genotype</i>	<i>Classification</i>	
CLCN7	Exon 5/25	ENST00000382745.4:c.376C>T ENSP00000372193.4:p.Arg126Cys Grch37 (hg19) chr16: 1510925 Grch38 (hg38) chr16: 1460924			Homozygous	Probably pathogenic variant Missense variant	

*Percentage of presentation of genes in malignant childhood osteopetrosis.

**Detected in our patient by genetic sequencing.

AR: autosomal recessive; AD: autosomal dominant.

Diagnosis

The diagnosis of childhood osteopetrosis is based on clinical and radiographic evaluations and confirmed by genetic testing². It is essential to consider the diagnosis based on clinical suspicion and corroborate it by radiography and image studies, where cortical atrophy and generalized sclerosis mainly affecting the skull, pelvis, and spine can be appreciated. The characteristic image of *bone within a bone*, particularly in vertebrae and phalanges, can be observed. Age of presentation, inheritance, and associated clinical features such as pancytopenia, neurodegeneration, mental retardation, tubular acidosis, neuronal compression, and visual and auditory impairment support the diagnosis.

In case of suspicion, laboratory studies should be requested, such as serum calcium, parathyroid hormone, phosphorus, creatinine, 25-hydroxyvitamin D, and lactic dehydrogenase levels, which provide mineral

homeostasis data. Also, a complete blood count with differential is necessary for bone marrow failure evaluation. Bone biopsy is useful for differentiating rich or deficit osteoclasts forms of osteopetrosis; however, it should not be performed routinely and is not essential for diagnosis.

Creatine kinase BB isoenzyme has been detected in patients with malignant osteopetrosis with CLCN-7 mutation; however, its levels do not correlate with the severity of the disease, and normal levels do not exclude the diagnosis⁸.

Finally, the specific mutation must be confirmed by genetic testing to provide follow-up, prognosis, a probable response to treatment, recurrence, and genetic counseling.

Multidisciplinary management of these patients is vital since multiple organs and systems are affected. Endocrinologically, serum calcium levels should be

monitored since bone cannot mobilize calcium due to the osteoclasts' defect, which causes hypocalcemia and, secondary to this, tetany and seizures.

It is necessary to periodically evaluate patients' visual capacity to detect and control the emergence of major visual complications, such as optic nerve atrophy. Patients often have dental abnormalities, such as delayed or failed tooth eruption, malformation, and easy teeth loss. Fractures and their complications with osteomyelitis are frequent. Therefore, an expert orthopedic surgeon should evaluate patients. Neurologically, developmental delay, compression neuropathies, and craniofacial deformities should be intentionally sought.

Regarding hearing, nerve compression can lead to sensorineural deafness. Concerning hematological complications, pancytopenia is the primary life-threatening condition of patients with osteopetrosis, leading to severe infections and bleeding⁵.

Differential diagnosis

The differential diagnosis should be made with any disease that causes bone sclerosis, such as berylliosis, myelofibrosis, Paget's disease, and malignant diseases. X-rays may show an increase in bone mineral density; however, compared to osteopetrosis, this alteration improves overtime. When osteopetrosis is diagnosed, it is essential to distinguish the subtype because each has a different evolution, progression, prognosis, and treatment.

Genetic alterations

The primary characteristic mutation of osteopetrosis is found in the TCIRG1 gene, which encodes the $\alpha 3$ subunit of the vacuolar H⁺ATPase (V-ATPase), which pumps protons through the membranes, helping to regulate cellular and extracellular pH.

The V-ATPase plays an essential role on the surface of osteoclasts. This protein is embedded in a membrane that contacts the bone's surface and forms a compartment between the osteoclast and the bone surface. Its function is to pump protons into the bone, acidifying it and creating a suitable bone resorption environment⁹. This mutation is responsible for 50% of patients diagnosed with recessive osteopetrosis¹⁰.

The CLCN7 gene encodes a chloride channel (CLC-7) that provides electroneutrality during the acidification process⁴. The mutation of this gene is present in 10-15% of patients with malignant osteopetrosis.

The third gene involved in this disease is OSTM1, which causes a more aggressive disease phenotype, shortening survival.

Treatment

HSCT is a procedure in which stem cells (HSC) from a disease-free donor are infused into patients with the disease. This procedure is performed to restore bone marrow function. There are different types of HSCT, depending on the type of HSC donor: autologous transplant (donor and recipient are the same subject), allogeneic transplant, which is performed from a donor with human leukocyte antigen (HLA) 100% compatible with the recipient and can be a related donor (family member) or an unrelated donor (non-family member), and haploidentical transplant, in which the family donor has an HLA 50% compatible with the recipient.

The initial treatment of osteopetrosis is mainly supportive and focuses on treating the main complications, such as pancytopenia, infections, and bleeding.

Fractures and arthritis require specialized treatment and follow-up since there is usually a delay in consolidation, osteomyelitis, and recurrent fractures.

Developmental delay and seizures associated with normal calcium levels often indicate childhood osteopetrosis. Neurological evaluations, including magnetic resonance imaging (MRI) and electroencephalogram, periodic ophthalmological examinations, including visual evoked potentials, and fundus examination to detect optic nerve atrophy, should be performed as soon as possible.

Hearing function evaluations should also be performed because, initially, neurosensory damage is mild; however, it may contraindicate HSCT as it progresses to severe forms.

Bone marrow failure can be treated initially with platelet and red blood cell concentrates transfusions; however, the definitive treatment of osteopetrosis is Allo-HSCT. In this pathology, HSCT is considered a therapeutic emergency because, as the disease progresses, sensory, visual, and hearing alterations become irreversible if treatment is late.

Transplant-related complications include transplant rejection, delayed graft function, hepatic sinusoidal occlusive syndrome, pulmonary hypertension, and hypercalcemic crises¹¹.

It is necessary to keep this disease under consideration when evaluating a patient with multiple dysmorphia, retarded growth and development, as well as sensory alterations, accompanied by metabolic and hematological alterations since timely diagnosis will

allow to perform an effective treatment and thus avoid a progression of the disease with more significant neurosensory impairment. Highlighting the importance of this pathology's treatment, we present the case of a patient with osteopetrosis treated with an Allo-HSCT, who had a successful evolution, even with a late disease diagnosis and a mild neurosensorial impairment.

Clinical case

We present the case of a 3-year and 2-month-old male patient from the State of Mexico. In his family medical history, healthy parents with no chronic degenerative diseases or consanguinity, a healthy 8-year-old sister, and no history of cancer, genetic or metabolic diseases, or immunodeficiency were reported.

At 1 year of age, the patient attended the Hospital Infantil de México Federico Gómez (HIMFG) for presenting community-acquired pneumonia (CAP), and later required hospitalizations for the same diagnosis (Fig. 1).

At 3 years of age, he was admitted again for CAP. On physical examination, generalized integument paleness, macrocephaly, hypertelorism, microretrognathia, prominent forehead, telecanthus, trichiasis, prominent eyes, flat nasal bridge, short neck, and narrow chest were observed. The skull X-ray showed the *mask* sign, characterized by generalized bone hyperdensity, predominantly at the base of the skull, which gave it the appearance of a mask in the orbital region. A chest X-ray was performed, observing an increase in bone density at the rib, sternal, and vertebral level. In addition, the *bone within a bone* sign, which consists of lines parallel to the tibia's cortical bone, was observed in the long bone X-ray. In laboratory studies, bicytopenia was reported in the complete blood count (hemoglobin 5.7 mg/dl, hematocrit 17.7%, leukocytes 13,400 cells/ μ L, total neutrophils 4020 cells/ μ L, and platelets 22,000 cells/ μ L). Therefore, as part of the approach, a bone marrow biopsy was requested, which reported hypocellularity, small intertrabecular spaces with fibrous tissue, and endochondral ossification. Due to the presence of dysmorphic syndrome, the patient required evaluation by the genetics service.

The patient was diagnosed with osteopetrosis at 3 years and 2 months of age, and as part of the evaluation by the HSCT service, the molecular study was carried out using second-generation sequencing in the HIMFG Research Unit. A mutation in the CLCN7 gene was reported, and the patient was classified as a homozygous genotype (Table 1). With this mutation, the patient met the criteria for an Allo-HSCT.

During hospitalization, the patient presented bilateral serous otitis media with secondary conductive hearing loss, for which ventilation tubes were placed. Influenza was detected, requiring antiviral treatment; another event of otitis media with otorrhea occurred, for which the patient required myringotomy and placement of ventilation tubes again.

A skull MRI was performed in the pre-transplant evaluations, where frank cortical atrophy with secondary ventricular dilation associated with its underlying pathology was observed. We detected a slight alteration in the bilateral visual pathways' conduction, together with a normal audiometry report, employing visual evoked potentials. Due to these results and the significant risk of developmental delay, the Infant Development Assessment test was performed, in which the patient met the criteria for risk of developmental delay. In the Battelle developmental test, a total development ratio of 63 was reported, corresponding to an equivalent age of 2 years and 3 months of age (deficit of 1 year and 5 months [37%]). Finally, the patient was diagnosed with global neurodevelopmental delay.

According to the HSCT protocol of the HIMFG, comorbidities were evaluated by the following services: ophthalmology, endocrinology, cardiology, infectology, otorhinolaryngology, pulmonology, nephrology and gastroenterology, and nutrition. Neurosensory, severe visual, or hearing damage were ruled out. In the admission blood count, before the HSCT, the following results were reported: total leukocytes 5300 cells/ μ L, total neutrophils 2070 cells/ μ L, platelets 35,000 cells/ μ L, and hemoglobin 9.1 mg/dL. At 3 years and 9 months of age, Allo-HSCT was performed from 100% compatible related donor (sister), using a myeloablative conditioning regimen: on days -7, -6, -5, and -4, the patient received busulfan (1.2 mg/kg/day), and on days -3 and -2, cyclophosphamide (60 mg/kg/day). Subsequently, a dose of 4.7×10^7 cells/kg obtained from bone marrow was infused.

As part of the prophylaxis for graft-versus-host disease (GvHD), immunosuppression was used based on cyclosporine (CsA, 3 mg/kg/day) and methotrexate (15 mg/m² day +1 and 10 mg/m² day on days +1, +3, +5, +7, and +11). However, due to the lack of graft data on day +22, the calcineurin inhibitor dose was decreased, continuing with stimulation using granulocyte stimulating factor (Filgrastim). On day +27, granulocytic graft data with a total neutrophil count of 1200/ μ L were observed. On day +35, the patient showed 100% chimerism. Therefore, the dose of Filgrastim was decreased, and treatment with platelet-stimulating factor (Eltrombopag) was added, which continued for 6 months.

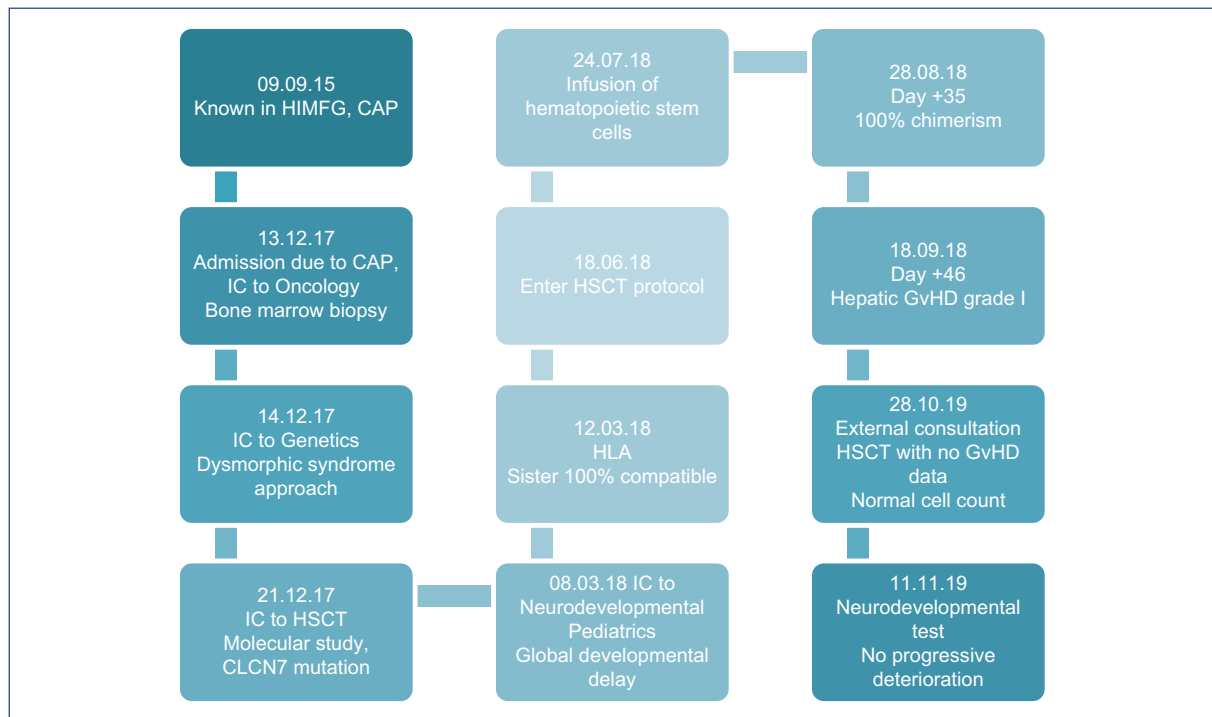


Figure 1. Chronological evolution of a patient with osteopetrosis. CAP: community-acquired pneumonia; GvHD: graft-versus-host disease; HIMFG: Hospital Infantil de México Federico Gómez; HLA: human leukocyte antigen; HSCT: hematopoietic stem cell transplantation; IC: interconsultation.

During this period, the patient developed pneumonitis—requiring supplemental oxygen support through nasal prongs and inhaled steroid management—and presented hypercalcemia and hyperphosphatemia—which responded to management with hydration, forced diuresis, and phosphorus chelator, with no other complications. Subsequently, on day +46, Grade II acute GvHD was diagnosed, supported by altered liver function tests with elevated bilirubin, for which treatment with methylprednisolone (1 mg/kg/day), cyclosporine, and ursodeoxycholic acid was administered. The treatment was gradually decreased according to the clinical course and CsA levels. Due to the adequate response to treatment, it was possible to withdraw immunosuppressive drugs (currently, the patient is not immunosuppressed).

According to the follow-up protocol, a periodic quantification of chimerism was carried out (on days +15, +21, +28, +35, +100, and +150) to verify the transplant graft. On day +15, a chimera of 16.6% was found; subsequently, on day +21, the percentage increased to 59.88%, and on days +35, +100, and +150 after HSCT, 100% chimerism was documented (Fig. 2). At present, at 5 years of age, the patient continues in monthly outpatient follow-up and is in the process of entering preschool education. Furthermore, cell numbers are normal, with no platelet-stimulating factor

or erythropoietin requirement, no GvHD data, and deferasirox treatment to avoid iron overload. Due to delayed growth, a weight of 14.2 kg (PZ -2), and a height of 90 cm (PZ -3) at 5 years and 3 months of age, the patient is being followed up by the endocrinology service. The patient maintains a visual capacity with a slight deficit but no progression and under ophthalmology service follow-up.

In addition, the patient undergoes an annual audiological evaluation, with no apparent deficit. As part of the follow-up, the EDI test that reported significant developmental delay improved compared to the previous results. An increase in the score of six evaluated domains was observed, finding that the personal-social and adaptive sphere significantly improved. Since the patient showed no added neurological deficit and an improvement was reported in neurodevelopmental tests, a new neurological imaging study was not considered necessary at the time. At present, the patient is being monitored by the neurodevelopment and neurology service.

Discussion

Infantile osteopetrosis is a rare hereditary disease, with a characteristic phenotype of short stature,

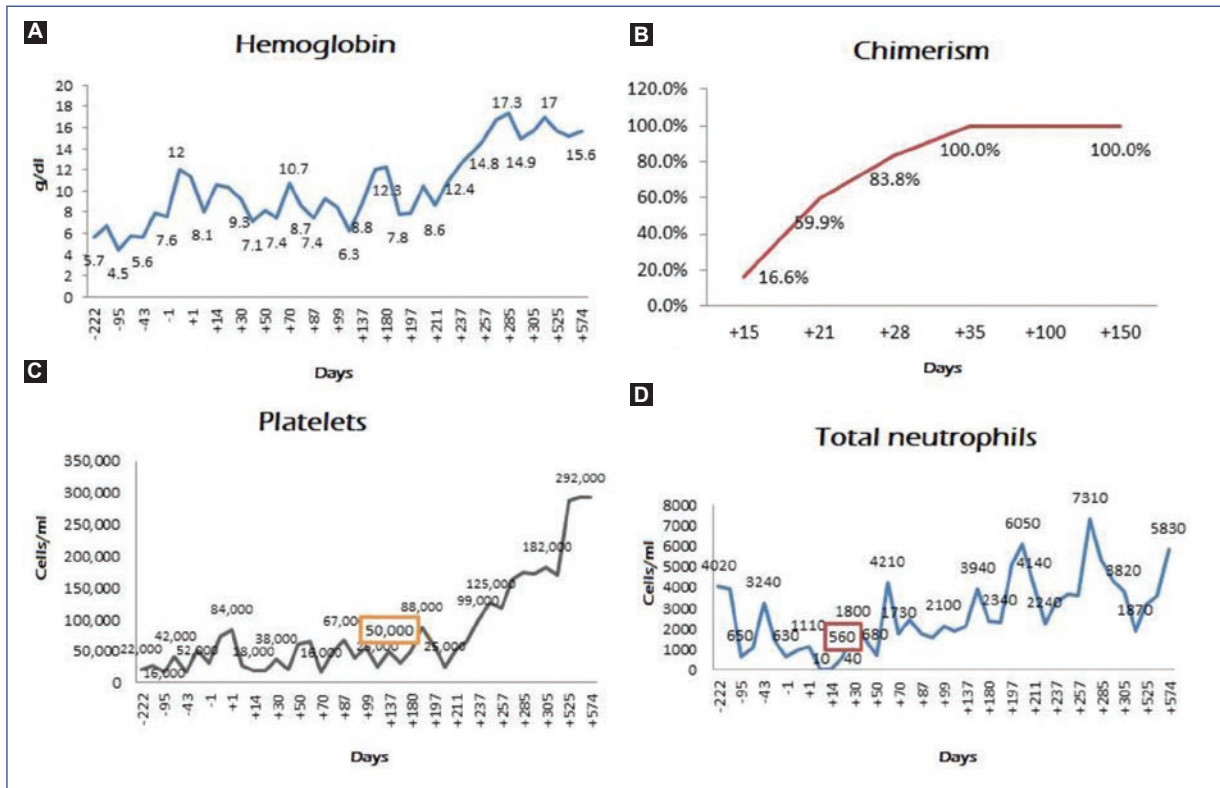


Figure 2. Laboratory studies of the patient with post-transplant osteopetrosis. **A.** Hemoglobin value after transplantation. **B.** Molecular chimerism after transplantation. **C.** Platelet value after transplantation. **D.** Granulocytic value after transplantation.

hypocalcemia, fractures, compression neuropathy, and pancytopenia; it is caused by the failure in the development and function of osteoclasts. We present the case of a 5-year-old male with a *CLCN7* gene mutation and a 1-year follow-up after Allo-HSCT. Because osteopetrosis is caused by a defect in the osteoclasts derived from the hematopoietic cell line, bone marrow transplantation is the definitive treatment. Our patient underwent Allo-HSCT at 3 years and 9 months of age and currently has normal cell counts. The skeletal deformities and bone sclerosis shown on the X-rays improved since treatment (Fig. 3). Since the first approach, this patient exceeded the 3-year life expectancy reported for osteopetrosis patients with the *CLCN-7* mutation (Table 1). Over 600 days after the transplant, the patient has shown a favorable evolution, decreasing the need for transfusions and hospitalization. Furthermore, skeletal deformities and neurodevelopmental tests have improved, leading to a better quality of life.

Severe osteopetrosis with increased bone mineral density results from the absence of osteoclasts, caused by a defect in the differentiation of osteoclast precursors or by dysfunctional osteoclasts. Therefore, the

definitive treatment must be the transplant of hematopoietic stem cells with a bone marrow origin to obtain bone marrow-derived osteoclasts.

Abnormal bone expansion interferes with hematopoiesis, causing life-threatening pancytopenia and extramedullary hematopoiesis in the spleen and liver, and frequent hepatosplenomegaly. This patient presented pancytopenia at diagnosis. Initially, an infiltrative syndrome was suspected but ruled out; later, osteopetrosis was diagnosed.

Patients with some mutation usually have neurosensory, visual, and auditory alterations caused by bone compression¹². In this patient, cortical atrophy accompanied with secondary ventricular dilation and bilateral visual pathway conduction alteration was documented, consistent with some reports in which MRIs show myelination delay and progressive cortical and subcortical atrophy¹³. The leading causes of death in these patients are infections, bleeding, and severe anemia, and allogeneic hematopoietic progenitor cells transplant is the only curative option¹⁴. A 5-year survival rate of 73% is reported when 100% compatible donor transplant is performed¹⁵. Risk of death increases in the first

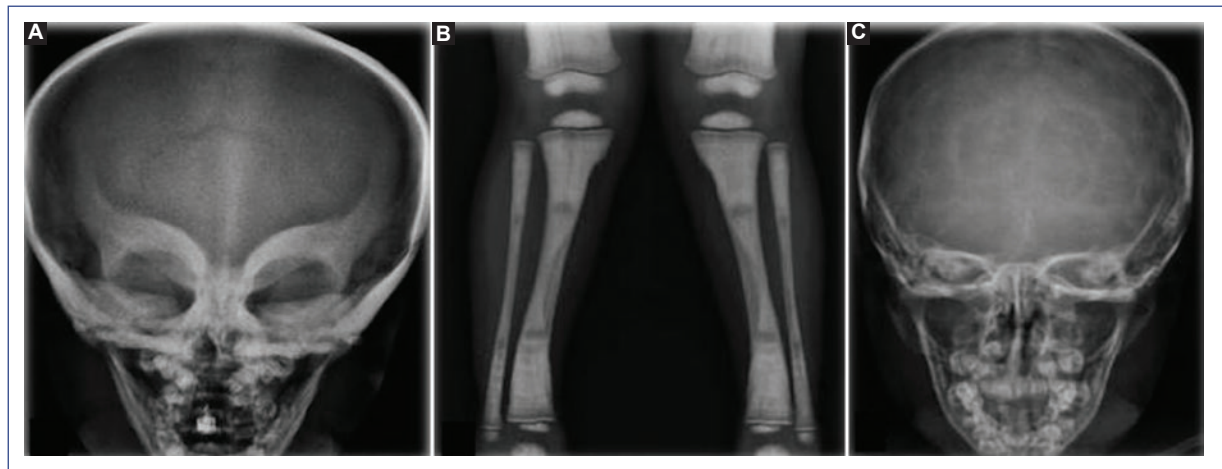


Figure 3. Osteopetrosis patient imaging studies. **A.** X-ray of the skull showing *mask* sign. Predominant generalized bone hyperdensity is observed at the base of the skull (before transplantation). **B.** X-ray of tibia and fibula with the *bone within a bone* sign. **C.** X-ray of the skull after transplantation with decreased bone hyperdensity.

10 years if Allo-HSCT is not performed due to the suppression of hematopoiesis in the bone marrow and its consequences.

The highest survival is reported in patients who received a transplant 100% HLA compatible of a related donor. The 5- and 10-year survival in patients with 100% compatible related donor Allo-HSCT is 62% in both, while for transplant of unrelated donor decreases to 42% and 39%, respectively. Therefore, it is of critical importance to obtain a related donor Allo-HSCT¹⁶. As for the complications that can occur after transplant in patients with osteopetrosis, primary and late graft failure has been described. In the present case, we observed delayed platelet engraftment with an adequate response to the platelet-stimulating factor. This complication imposes a higher mortality risk in transplanted patients¹⁷.

The leading cause of transplant-related mortality is graft failure, accounting for 50% of deaths in transplants from related donors and 43% from unrelated donors.

Allo-HSCT improves bone lesions within 2 months, and they resolve entirely within a year of transplant¹⁸. However, survivors reported that only 7% experience improvement regarding the optical damage, 69% show no progression, and 25% show deterioration.

This clinical case generates essential information about HSCT and osteopetrosis despite the age at the time of diagnosis because the evolution has been favorable. Therefore, we emphasize the importance of clinical suspicion for timely diagnosis and treatment. As no documented evidence exists in our country, it is

imperative to generate this kind of reports due to the remarkable improvement that a timely treatment means in patients' quality of life and survival.

There is only one previous report in our country, documenting a 9-month-old patient who required a second transplant at 13 months of age, using the umbilical cord as a cellular source on both occasions¹⁹. It is necessary to continue investigating and reporting these cases to enrich this knowledge.

In this case, we emphasize the importance of early diagnosis. Suspicion of the disease in a patient with pancytopenia, craniofacial and thoracic dysmorphism, hepatosplenomegaly, and radiological evidence of bone sclerosis should prompt a comprehensive approach and early osteopetrosis diagnosis. Therefore, timely interventions and early treatment with Allo-HSCT could be established to improve the patient's clinical conditions. It is essential to perform an Allo-HSCT, preferably before 1 year of age, to avoid progressive and irreversible neurological damage and decrease mortality. It has been shown that patients who have 100% compatible donor for Allo-HSCT have a 5-year survival of 73%. However, with an unrelated donor, survival of 40% has been reported.

Timely Allo-HSCT has an impact on the patient's prognosis and quality of life. It is possible to perform late Allo-HSCT in a patient with mild neurosensory deficits and achieve a cure for osteopetrosis, stop the progression of neurological damage, and achieve an adequate quality of life on the condition where a multidisciplinary treatment is available.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on patient data publication.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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